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 NEWS  1          Web Page for STN Seminar Schedule - N. America
 NEWS  2  AUG 06  CAS REGISTRY enhanced with new experimental property tags
 NEWS  3  AUG 06  FSTA enhanced with new thesaurus edition
 NEWS  4  AUG 13  CA/CAplus enhanced with additional kind codes for granted
                  patents
 NEWS  5  AUG 20  CA/CAplus enhanced with CAS indexing in pre-1907 records
 NEWS  6  AUG 27  Full-text patent databases enhanced with predefined
                  patent family display formats from INPADOCDB
 NEWS  7  AUG 27  USPATOLD now available on STN
 NEWS  8  AUG 28  CAS REGISTRY enhanced with additional experimental
                  spectral property data
 NEWS  9  SEP 07  STN AnaVist, Version 2.0, now available with Derwent
                  World Patents Index
 NEWS 10  SEP 13  FORIS renamed to SOFIS
 NEWS 11  SEP 13  INPADOCDB enhanced with monthly SDI frequency
 NEWS 12  SEP 17  CA/CAplus enhanced with printed CA page images from
                  1967-1998
 NEWS 13  SEP 17  CAplus coverage extended to include traditional medicine
                  patents
 NEWS 14  SEP 24  EMBASE, EMBAL, and LEMBASE reloaded with enhancements
 NEWS 15  OCT 02  CA/CAplus enhanced with pre-1907 records from Chemisches
                  Zentralblatt
 NEWS 16  OCT 19  BEILSTEIN updated with new compounds
 NEWS 17  NOV 15  Derwent Indian patent publication number format enhanced
 NEWS 18  NOV 19  WPIX enhanced with XML display format
 NEWS 19  NOV 30  ICSD reloaded with enhancements
 NEWS 20  DEC 04  LINPADOCDB now available on STN
 NEWS 21  DEC 14  BEILSTEIN pricing structure to change
 NEWS 22  DEC 17  USPATOLD added to additional database clusters
 NEWS 23  DEC 17  IMSDRUGCONF removed from database clusters and STN
 NEWS 24  DEC 17  DGENE now includes more than 10 million sequences
 NEWS 25  DEC 17  TOXCENTER enhanced with 2008 MeSH vocabulary in
                  MEDLINE segment
 NEWS 26  DEC 17  MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
 NEWS 27  DEC 17  CA/CAplus enhanced with new custom IPC display formats
 NEWS 28  DEC 17  STN Viewer enhanced with full-text patent content
                  from USPATOLD
 NEWS 29  JAN 02  STN pricing information for 2008 now available
 NEWS 30  JAN 16  CAS patent coverage enhanced to include exemplified
                  prophetic substances
 NEWS 31  JAN 28  USPATFULL, USPAT2, and USPATOLD enhanced with new
                  custom IPC display formats
 NEWS 32  JAN 28  MARPAT searching enhanced
 NEWS 33  JAN 28  USGENE now provides USPTO sequence data within 3 days
                  of publication
 NEWS 34  JAN 28  TOXCENTER enhanced with reloaded MEDLINE segment
 NEWS 35  JAN 28  MEDLINE and LMEDLINE reloaded with enhancements
 NEWS 36  FEB 08  STN Express, Version 8.3, now available


 NEWS EXPRESS FEBRUARY 08 CURRENT WINDOWS VERSION IS V8.3,
              AND CURRENT DISCOVER FILE IS DATED 24 JANUARY 2008

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 NEWS IPC8      For general information regarding STN implementation of IPC 8

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FILE 'BIOSIS' ENTERED AT 13:10:56 ON 11 FEB 2008
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=> NNRTI
L1        2002 NNRTI

=> resistant
L2      894769 RESISTANT

=>
=> 1 and L2
L3      405611 1 AND L2

=> L1 and L2
L4         546 L1 AND L2

=> codon and L4
L5          34 CODON AND L4

=> V245E
L6           0 V245E

=> D L5 IBIB ABS 1-34 TI

L5   ANSWER 1 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2007:3033  CAPLUS
DOCUMENT NUMBER:         147:137763
TITLE:                   Genotype and phenotype patterns of drug-
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resistant HIV-1 subtype B' (thai B) isolated from patients failing antiretroviral therapy in China

AUTHOR(S): Ma, Liying; Sun, Jianping; Xing, Hui; Si, Xuefeng; Yuan, Lin; Guo, Yanfang; Cheng, Hua; Shao, Yiming

CORPORATE SOURCE: State Key Laboratory for Infection Diseases Prevention and Control, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention (China CDC), Beijing, 100050, Peop. Rep. China

SOURCE: JAIDS, Journal of Acquired Immune Deficiency Syndromes (2006), Volume Date 2007, 44(1), 14-19
CODEN: JJASFJ; ISSN: 1525-4135

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Many AIDS patients in China who received free-of-charge antiretroviral therapeutics, including nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), showed significant life improvement. Increasing nos. of patients, however, are experiencing antiretroviral therapy failure due to the emergence of drug-resistant viruses. The aim of this study was to investigate the genotypic and phenotypic drug resistance patterns of HIV-1 subtype B' variants, which are prevalent in China, in order to rationally design more efficient anti-HIV-1 regimens for future treatment of AIDS patients. 13 out of 16 patients (81%) who were treated with two NRTIs (ddI, and d4T or AZT) and one NNRTI (NVP) exhibited high resistance to NVP, 8 of them with a >1000 IC50 fold increase. Five codons (101, 103, 108, 181, and 190) were involved in the NVP-resistant mutations, and K103N and Y181C mutations were predominant in these isolates. Fifteen isolates were resistant to at least one of the NRTIs, with high resistance to AZT (>10 IC50 fold increase) and intermediate resistance to d4T or ddI (.apprx.4 IC50 fold increase). More than 10 codons were involved in the NRTI-resistant mutation and located in two regions (M41-V75 and T215-K219) of the reverse transcriptase. Concordance between the genotype and phenotype patterns for both NRTIs and NNRTI were detected in a majority of the isolates, suggesting that phenotypic resistance is predictable from genotyping assays, which are faster and less expensive than phenotypic assay. Because NVP and AZT can induce high resistances in these patients, these two drugs should be replaced with others more effective NNRTIs and NRTIs.

TI Genotype and phenotype patterns of drug-resistant HIV-1 subtype B' (thai B) isolated from patients failing antiretroviral therapy in China

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 34 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:334033 CAPLUS

DOCUMENT NUMBER: 145:305690

TITLE: Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother-to-child HIV transmission

AUTHOR(S): Loubser, Shayne; Balfe, Peter; Sherman, Gayle; Hammer, Scott; Kuhn, Louise; Morris, Lynn

CORPORATE SOURCE: AIDS Virus Research Unit, National Institute for Communicable Diseases, Johannesburg, S. Afr.

SOURCE: AIDS (Hagerstown, MD, United States) (2006), 20(7), 995-1002
CODEN: AIDSET; ISSN: 0269-9370

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

```
AB   Objectives: Single-dose nevirapine (sd-NVP) for prevention of
     mother-to-child HIV-1 transmission is associated with selection of
     resistant viral variants, particularly the Lysine (K) to
     Asparagine (N) mutation at codon 103 (K103N) of reverse
     transcriptase.  As this may influence subsequent treatment responses, a
     better understanding of the dynamics of decay and persistence of this
     variant is needed.  Design and methods: We measured the frequency of K103N
     mutants among a cohort of HIV-1-infected pregnant women recruited at an
     out-patient clinic in Johannesburg, South Africa.  Samples taken 6 wk, 3,
     7 and 12 mo after delivery from 67 HIV-1-infected women who received
     sd-NVP during labor to prevent transmission were analyzed.  Quantification
     of K103N mutants in maternal plasma viral RNA and cellular DNA was done
     using an allele-specific real-time polymerase chain reaction assay capable
     of detecting codons AAC and AAT if their frequency was > 0.002
     of the total viral population.  Results: Using the allele-specific assay,
     87.1% (27/31) of RNA samples and 52.3% (23/44) of DNA samples collected 6
     wk after sd-NVP had detectable K103N variants.  This declined to 65.4%
     (17/26), 38.9% (14/36), and 11.3% (6/53) in RNA at 3, 7 and 12 mo resp.,
     and to 4.2% (2/48) in DNA at 12 mo.  Conclusions: K103N resistant
     variants were present in almost all women at 6 wk post-sd-NVP but declined
     rapidly over time.  Resistant variants were detected less
     frequently in cellular DNA with persistence in this compartment by 12 mo
     post-sd-NVP among only a minority.
TI   Decay of K103N mutants in cellular DNA and plasma RNA after single-dose
     nevirapine to reduce mother-to-child HIV transmission
REFERENCE COUNT:         19    THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 3 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2006:197556  CAPLUS
DOCUMENT NUMBER:         145:388729
TITLE:                   Selection and persistence of non-nucleoside reverse
                         transcriptase inhibitor-resistant HIV-1 in
                         patients starting and stopping non-nucleoside therapy
AUTHOR(S):               Palmer, Sarah; Boltz, Valerie; Maldarelli, Frank;
                         Kearney, Mary; Halvas, Elias K.; Rock, Diane; Falloon,
                         Judith; Davey, Richard T., Jr.; Dewar, Robin L.;
                         Metcalf, Julia A.; Mellors, John W.; Coffin, John M.
CORPORATE SOURCE:        HIV Drug Resistance Program, National Cancer
                         Institute, National Institutes of Health, Frederick,
                         MD, USA
SOURCE:                  AIDS (Hagerstown, MD, United States) (2006), 20(5),
                         701-710
                         CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER:               Lippincott Williams & Wilkins
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Understanding the selection and decay of drug-resistant HIV-1
     variants is important for designing optimal antiretroviral therapy.  The
     objective was to develop a high-throughput, real-time reverse
     transcriptase (RT) polymerase chain reaction (PCR) assay to quantify
     non-nucleoside reverse transcriptase inhibitor (NNRTI)-
     resistant variants K103N (AAT or AAC alleles) at frequencies as
     low as 0.1%, and to apply this to monitor these variants before, during,
     and after NNRTI therapy.  HIV-1 RNA in longitudinal plasma
     samples obtained from patients starting and stopping NNRTI
     therapy was converted to cDNA and the target sequence region amplified and
     quantified by real-time PCR.  Approx. 10 copies/reaction provided a
     template for a second round of PCR using primers that discriminated
     between the mutant and wild-type alleles.  Amplification specificity was
     confirmed by thermal denaturation anal.  Frequencies of 103N similar to
     assay background (0.029%) were observed in longitudinal samples from 9 of 12
     treatment-naive patients; three patients had transient increases in 103N
     frequency to a range of 0.21-0.48%, which was 7-16.5 times assay
     background.  Anal. of longitudinal plasma samples from six NNRTI
     -experienced patients showed three patterns: persistence of 103N variants
     after stopping NNRTI therapy, codon switching of 103N
     between AAC and AAT during NNRTI therapy, and decay of 103N
     variants to below assay background after cessation of NNRTI
     therapy.  Allele-specific RT-PCR quantified the emergence and decay of
     drug-resistant variants in patients over a broad range of
     frequencies (0.1-100%).  The rate of decay of K103N variants after
     stopping NNRTI therapy was highly variable.
TI   Selection and persistence of non-nucleoside reverse transcriptase
     inhibitor-resistant HIV-1 in patients starting and stopping
     non-nucleoside therapy
REFERENCE COUNT:         46    THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 4 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2006:78315  CAPLUS
DOCUMENT NUMBER:         145:227326
TITLE:                   Prevalence and evolution of drug resistance HIV-1
                         variants in Henan, China
AUTHOR(S):               Li, Jing Yun; Li, Han Ping; Li, Lin; Li, Hong; Wang,
                         Zhe; Yang, Kun; Bao, Zuo Yi; Zhuang, Dao Min; Liu, Si
                         Yang; Liu, Yong Jian; Xing, Hui; Shao, Yi Ming
CORPORATE SOURCE:        AIDS Research Department, Institute of Microbiology
                         and Epidemiology, Academy of Military Medical Science,
                         Beijing, 100071, Peop. Rep. China
SOURCE:                  Cell Research (2005), 15(11-12), 843-849
                         CODEN: CREEB6; ISSN: 1001-0602
PUBLISHER:               Editorial Office of Cell Research
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   To understand the prevalence and evolution of drug resistant HIV
     strains in Henan China after the implementation of free antiretroviral
     therapy for AIDS patients.  45 Drug naive AIDS patients, 118 AIDS patients
     who received three months antiretroviral therapy and 124 AIDS patients who
     received six months antiretroviral treatment were recruited in the
     southern part of Henan province.  Information on general condition,
     antiretroviral medicines, adherence and clin. syndromes were collected by
     face to face interview.  Meanwhile, 14mL EDTA anticoagulant blood was
     drawn.  CD4/CD8 T cell count, viral load and genotypic drug resistance
     were tested.  The rates of clin. improvement were 55.1% and 50.8% resp.
     three months and six months after antiretroviral therapy.  The mean CD4
     cell count after antiretroviral therapy was significantly higher than in
     drug naive patients.  The prevalence rate of drug resistant HIV
     strains were 13.9%, 45.4% and 62.7% in drug naive patients, three month
     treatment patients and six month treatment patients, resp.  The number of
     resistance mutation codons and the frequency of mutations
     increased significantly with continued antiretroviral therapy.  The
     mutation sites were primarily at the 103, 106 and 215 codons in
     the three-month treatment group and they increased to 15 codon
     mutations in the six-month treatment group.  From this result, the
     evolution of drug resistant strains was inferred to begin with
     the high level NNRTI resistant strain, and then
     develop low level resistant strains to NRTIs.  The HIV strains
     with high level resistance to NVP and low level resistance to AZT and DDI
     were highly prevalent because of the AZT+DDI+NVP combination therapy.
     These HIV strains were also cross resistant to DLV, EFV, DDC and
     D4T.  Poor adherence to therapy was believed to be the main reason for the
     emergence and prevalence of drug resistant HIV strains.  The
     prevalence of drug resistant HIV strains was increased with the
     continuation of antiretroviral therapy in the southern part of Henan
     province.  Measures, that could promote high level adherence, provide new
     drugs and change ART regimens in failing patients, should be implemented
     as soon as possible.
TI   Prevalence and evolution of drug resistance HIV-1 variants in Henan, China
REFERENCE COUNT:         18    THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 5 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2006:19603  CAPLUS
DOCUMENT NUMBER:         144:205226
TITLE:                   Mutations other than 103N in human immunodeficiency
                         virus type 1 reverse transcriptase (RT) emerge from
                         K103R polymorphism under non-nucleoside RT inhibitor
                         pressure
AUTHOR(S):               Gatanaga, Hiroyuki; Hachiya, Atsuko; Kimura, Satoshi;
                         Oka, Shinichi
CORPORATE SOURCE:        AIDS Clinical Center, International Medical Center of
                         Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo, 162-8655,
                         Japan
SOURCE:                  Virology (2006), 344(2), 354-362
                         CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER:               Elsevier
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   K103N mutation in human immunodeficiency virus type 1 (HIV-1) reverse
     transcriptase (RT) confers high-level resistance against non-nucleoside RT
     inhibitors (NNRTIs) and it easily occurs partly because it
     arises by a single nucleotide substitution from wild-type K103.  There are
     polymorphisms at codon 103 of HIV-1 RT.  We found K103R
     polymorphic mutation in 3.3% of treatment-naive HIV-1-infected patients.
     R103N does not seem to occur as easily as K103N because R103N requires two
     nucleotide substitutions.  To induce NNRTI resistance-associated
     mutations, HIV-1K103R was propagated in the presence of increasing concns.
     of efavirenz (EFV) or nevirapine (NVP).  V179D emerged in all three EFV
     cultures and in two of four NVP cultures.  R103G emerged by a single
     nucleotide substitution in one of three EFV cultures.  R103N did not
     emerge in any of 7 NNRTI cultures.  Anal. of recombinant HIV-1s
     showed that HIV-1K103R/V179D was significantly resistant and
     HIV-1K103G was moderately resistant against EFV and NVP.
TI   Mutations other than 103N in human immunodeficiency virus type 1 reverse
     transcriptase (RT) emerge from K103R polymorphism under non-nucleoside RT
     inhibitor pressure
REFERENCE COUNT:         26    THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 6 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2005:1207309  CAPLUS
DOCUMENT NUMBER:         144:266630
TITLE:                   HIV-1 drug resistance in Thailand: Before and after
                         National Access to Antiretroviral Program
AUTHOR(S):               Sutthent, Ruengpung; Arworn, Daungnapa; Kaoriangudom,
                         Surapol; Chokphaibulkit, Kulkanya; Chaisilwatana,
                         Pongsakdi; Wirachsilp, Piyanot; Thiamchai, Vipa;
                         Sirapraphasiri, Thaweesarp; Tanprasertsuk, Sombat
CORPORATE SOURCE:        National HIV Repository and Bioinformatic Center
                         (Thailand), Department of Microbiology, Faculty of
                         Medicine Siriraj Hospital, Mahidol University,
                         Bangkok, 10700, Thailand
SOURCE:                  Journal of Clinical Virology (2005), 34(4), 272-276
                         CODEN: JCVIFB; ISSN: 1386-6532
PUBLISHER:               Elsevier B.V.
```

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: The Ministry of Public Health (Thailand), MoPH, has had a program called National Access to Antiretroviral Program for People who have AIDS (PHA) or "NAPHA", to offer free antiretroviral drugs (ARV), which are locally produced in Thailand, to any HIV-1 infected patients with CD4 < 200 since 2002. This program may increase usage of ARV therapy and the emergence of HIV-1 drug resistance. Objectives: To monitor HIV-1 ARV drug resistant codon mutation in Thailand before and after the "NAPHA" program. Materials and methods: EDTA blood samples were collected from 542 HIV-1 infected subjects, who received ARV therapy in 1999 and 2001-2003, and perinatal chemoprophylaxis in 1998 and 2000. HIV-1 pol nucleotide sequences were analyzed. Results: The percentage of drug resistant detection from the ARV therapy group in 1999 and 2001-2003 were 12.14 (34/280), 10.23 (9/88), 86.96 (20/23) and 57.55 (61/106), resp. Of 332 NRTI drug resistant codon mutation, 226 (68.07%) were thymidine analog mutations (TAMs). The percentage of TAMs detection in 1999 and 2001-2003 were 7.14 (20/280), 9.09 (8/88), 56.52 (13/23) and 43.34 (46/106), resp. Of 105 NNRTI drug resistant codon mutation, 95 (90.48%) were related to nevirapine drug resistance. Conclusion: Thailand may need more appropriate monitoring of drug resistance in the free ARV therapy program to protect the future usage of drugs by minimizing the emergence of drug resistance.

TI HIV-1 drug resistance in Thailand: Before and after National Access to Antiretroviral Program

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 34 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:991730 CAPLUS
DOCUMENT NUMBER: 143:341640
TITLE: The role of Thr139 in the human immunodeficiency virus type 1 reverse transcriptase sensitivity to (+)-calanolide A
AUTHOR(S): Auwerx, Joeri; Rodriguez-Barrios, Fatima; Ceccherini-Silberstein, Francesca; San-Felix, Ana; Velazquez, Sonsoles; De Clercq, Erik; Camarasa, Maria-Jose; Perno, Carlo-Federico; Gago, Federico; Balzarini, Jan
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, Belg.
SOURCE: Molecular Pharmacology (2005), 68(3), 652-659
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The coumarins represent a unique class of non-nucleoside reverse transcriptase inhibitors (NNRTIs) that were isolated from tropical plants. (+)-Calanolide A, the most potent compound of this class, selects for the T139I resistance mutation in HIV-1 reverse transcriptase (RT). Seven RTs mutated at amino acid position 139 (Ala, Lys, Tyr, Asp, Ile, Ser, and Gln) were constructed by site-directed mutagenesis. The mutant T139Q enzyme retained full catalytic activity compared with wild-type RT, whereas the mutant T139I, T139S, and T139A RTs retained only 85 to 50% of the activity. Mutant T139K, T139D, and T139Y RTs had seriously impaired catalytic activities. The mutations in the T139I and T139D RTs were shown to destabilize the RT heterodimer. (+)-Calanolide A lost inhibitory activity (up to 20-fold) against the mutant T139Y, T139Q, T139K, and T139I enzymes. All of the mutant enzymes retained marked susceptibility toward the other NNRTIs, including nevirapine,

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     delavirdine, efavirenz, thiocarboxanilide UC-781, quinoxaline GW867420X,
     TSAO [[2',5'-bis-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]-3'-
     spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide)] derivs., and the
     nucleoside inhibitor, ddGTP.  The fact that the T139I RT 1) proved to be
     resistant to (+)-calanolide A, 2) represents a catalytically
     efficient enzyme, and 3) requires only a single transition point mutation
     (ACA→ATA) in  codon 139 seems to explain why mutant T139I
     RT virus strains, but not virus strains containing other amino acid changes at
     this position, predominantly emerge in cell cultures under (+)-calanolide
     A pressure.
TI   The role of Thr139 in the human immunodeficiency virus type 1 reverse
     transcriptase sensitivity to (+)-calanolide A
REFERENCE COUNT:         38    THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 8 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2004:54691  CAPLUS
DOCUMENT NUMBER:         140:70393
TITLE:                   Evolution of human immunodeficiency virus type 1
                         (HIV-1) resistance mutations in nonnucleoside reverse
                         transcriptase inhibitors (NNRTIs) in
                         HIV-1-infected patients switched to antiretroviral
                         therapy without NNRTIs
AUTHOR(S):               Joly, Veronique; Descamps, Diane; Peytavin, Gilles;
                         Touati, Fatiha; Mentre, France; Duval, Xavier;
                         Delarue, Severine; Yeni, Patrick; Brun-vezinet,
                         Francoise
CORPORATE SOURCE:        Service des Maladies Infectieuses et Tropicales A,
                         Hopital Bichat Claude Bernard, Paris, 75877/18, Fr.
SOURCE:                  Antimicrobial Agents and Chemotherapy (2004), 48(1),
                         172-175
                         CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER:               American Society for Microbiology
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Authors studied the evolution of nonnucleoside reverse transcriptase
     inhibitor (NNRTI) resistance mutations among 29 human
     immunodeficiency virus type 1 (HIV-1)-infected patients who experienced
     virol. failure when receiving an NNRTI-containing regimen
     (nevirapine, delavirdine, or efavirenz) and subsequently switched to
     antiretroviral therapy without NNRTIs.  Genotypic resistance was
     determined from plasma samples collected at the time of NNRTI
     withdrawal (baseline) and during follow-up.  At baseline, 83% of patients
     had more than two thymidine analog resistance mutations (TAMs), and all
     had NNRTI resistance mutations.  Mutations at codons
     103, 181, and 190 were found in 62, 62, and 34% of the patients, resp.
     Follow-up samples were available after a median time of 6 mo in all
     patients and at 12 mo in 22 patients.  The mean number of resistance
     mutations to NNRTIs was significantly lower at months 6
     (1.34±1.04) and 12 (1.18±1.05) than at month 0 (2.03±1.02) (P <
     0.009).  The percentages of patients with at least one NNRTI
     resistance mutation were 100, 76, and 73% at baseline, month 6, and month
     12, resp. (P < 0.0044).  Overall, 70% of the patients had a mutation at
     codon 103 or 181 at month 12.  The mean number of TAMs did not vary
     significantly during follow-up.  Our data show that, in the context of
     maintained antiretroviral therapy, NNRTI resistance mutations
     persist in two-thirds of the patients in spite of NNRTI
     withdrawal.  These results argue for the low impact of NNRTI
     resistance mutations on viral fitness and suggest that resistance
     mutations to different classes of drugs are associated on the same genome, at
     least in some of the resistant strains.
TI   Evolution of human immunodeficiency virus type 1 (HIV-1) resistance
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     mutations in nonnucleoside reverse transcriptase inhibitors (
     NNRTIs) in HIV-1-infected patients switched to antiretroviral
     therapy without NNRTIs
REFERENCE COUNT:         21    THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 9 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2003:833636  CAPLUS
DOCUMENT NUMBER:         139:345392
TITLE:                   Human immunodeficiency virus type 1: Drug resistance
                         in treated and untreated Brazilian children
AUTHOR(S):               Simonetti, S. R. R.; Schatzmayr, H. G.; Simonetti, J.
                         P.
CORPORATE SOURCE:        Nucleo de Retrovirus, Departamento de Virologia,
                         Instituto Oswaldo Cruz-Fiocruz, Rio de Janeiro,
                         21045-900, Brazil
SOURCE:                  Memorias do Instituto Oswaldo Cruz (2003), 98(6),
                         831-837
                         CODEN: MIOCAS; ISSN: 0074-0276
PUBLISHER:               Instituto Oswaldo Cruz
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Twenty-two vertically human immunodeficiency virus type 1 (HIV-1) infected
     Brazilian children were studied for antiretroviral drug resistance.  They
     were separated into 2 groups according to the administration of antiretroviral
     therapy into those who presented disease symptoms or without symptoms and
     no therapy.  Viral genome sequencing reactions were loaded on an automated
     DNA sampler (TruGene, Visible Genetics) and compared to a database of wild
     type HIV-1.  In the former group 8 of 12 children presented isolates with
     mutations conferring resistance to protease inhibitors (PIs), 7 presented
     isolates resistant to nucleoside reverse transcriptase
     inhibitors (NRTIs) and 2 presented isolates resistant to
     non-nucleoside reverse transcriptase inhibitors (NNRTIs).  Ten
     children were included in the antiretroviral naive group.  Eight were
     susceptible to NRTIs and all of them were susceptible to PIs; one
     presented the V108I mutation, which confers low-level resistance to
     NNRTIs.  The data report HIV mutant isolates both in treated and
     untreated infants.  However, the frequency and the level of drug
     resistance were more frequent in the group receiving antiretroviral
     therapy, corroborating the concept of selective pressure acting on the
     emergence of resistant viral strains.  The children who
     presented alterations at polymorphism sites should be monitored for the
     development of addnl. mutations occurring at relevant resistance
     codons.
TI   Human immunodeficiency virus type 1: Drug resistance in treated and
     untreated Brazilian children
REFERENCE COUNT:         40    THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 10 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2003:759633  CAPLUS
DOCUMENT NUMBER:         140:209959
TITLE:                   Drug Resistance Profiles of Recombinant Reverse
                         Transcriptases from Human Immunodeficiency Virus Type
                         1 Subtypes A/E, B, and C
AUTHOR(S):               Quan, Yudong; Brenner, Bluma G.; Marlink, Richard G.;
                         Essex, Max; Kurimura, Takashi; Wainberg, Mark A.
CORPORATE SOURCE:        Lady Davis Institute, McGill University AIDS Centre,
                         Montreal, QC, H3T, Can.
SOURCE:                  AIDS Research and Human Retroviruses (2003), 19(9),
                         743-753
                         CODEN: ARHRE7; ISSN: 0889-2229
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PUBLISHER:               Mary Ann Liebert, Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   We have expressed purified recombinant reverse transcriptase (RT) from
     clin. isolates of human immunodeficiency virus subtypes B, C, and A/E in
     Escherichia coli.  The drug sensitivities of these RTs were then determined for
     both nucleoside RT inhibitors (NRTIs) and nonnucleoside RT inhibitors (
     NNRTIs) in cell-free RT assays.  Although A/E and C viruses
     contained numerous polymorphisms relative to subtype B (i.e., naturally
     occurring variations unrelated to drug resistance), the wild-type enzymes
     prepared from these or subtype A/E clin. isolates displayed <2-fold
     differences in drug sensitivities with regard to the active triphosphate
     active forms of NRTIs, as compared with RT expressed from BH-10
     recombinant virus.  Recombinant RTs from clin. isolates of subtypes B, C,
     and A/E that contained multiple resistance-associated mutations displayed
     expected variations in levels of resistance to the intracellular active
     forms of 3TC, ddI, ddC, and PMPA, i.e., 3TCTP, ddATP, ddCTP, and PMPApp,
     resp.  Subtype A/E and C RT enzymes contained only minor NNRTI
     polymorphisms that distinguished them from wild-type subtype B enzymes and
     wild-type RTs from these various subtypes showed only 1- to 4-fold
     variability in IC50 values for each of nevirapine (NVP), delavirdine
     (DLV), efavirenz (EFV), and calanolide A. In contrast, RT enzymes from
     subtype B and C viruses harboring specific NNRTI mutations were
     highly resistant to all four tested NNRTIs.  Subtype C
     variants containing the novel V106M resistance codon showed
     cross-resistance to all approved NNRTIs in cell-free RT assays.
TI   Drug Resistance Profiles of Recombinant Reverse Transcriptases from Human
     Immunodeficiency Virus Type 1 Subtypes A/E, B, and C
REFERENCE COUNT:         34    THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 11 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2002:280294  CAPLUS
DOCUMENT NUMBER:         137:231140
TITLE:                   Mutations associated with genotypic resistance to
                         antiretroviral therapy in treatment naive HIV-1
                         infected patients in Greece
AUTHOR(S):               Magiorkinis, E.; Paraskevis, D.; Magiorkinis, G.;
                         Chryssou, S.; Chini, M.; Lazanas, M.; Paparizos, V.;
                         Saroglou, G.; Antoniadou, A.; Giamarellou, E.;
                         Karafoulidou, A.; Hatzakis, A.
CORPORATE SOURCE:        Athens School of Medicine, National Retrovirus
                         Reference Center, Department of Hygiene and
                         Epidemiology, University of Athens, Athens, GR-115 27,
                         Greece
SOURCE:                  Virus Research (2002), 85(1), 109-115
                         CODEN: VIREDF; ISSN: 0168-1702
PUBLISHER:               Elsevier Science Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The widespread use of antiviral drugs against HIV has increased the
     prevalence of HIV-1 resistant strains among naive individuals
     due to transmission of resistant strains.  The purpose of this
     study was to investigate the presence of HIV-1 strains harboring
     resistance mutations in naive patients in Greece.  Blood samples were
     collected from 25 individuals.  The DNA sequence of protease and partial
     reverse transcriptase regions (codons 41-223) were obtained by
     direct sequencing.  Our results showed the absence of any primary
     resistance mutations in the studied population.  However, we were able to
     identify high prevalence of sequence polymorphisms at positions in reverse
     transcriptase region associated mainly with resistance to NNRTIs.
     Moreover, in protease region several secondary mutations were detected,
     suggesting the higher genetic variability of this region.  The clin.
     significance of the polymorphisms associated with reduced susceptibility to
     NNRTIs remains to be clarified.
TI   Mutations associated with genotypic resistance to antiretroviral therapy
     in treatment naive HIV-1 infected patients in Greece
REFERENCE COUNT:         27    THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 12 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2002:128778  CAPLUS
DOCUMENT NUMBER:         137:195021
TITLE:                   Dioxolane guanosine, the active form of the prodrug
                         diaminopurine dioxolane, is a potent inhibitor of
                         drug-resistant HIV-1 isolates from patients
                         for whom standard nucleoside therapy fails
AUTHOR(S):               Mewshaw, Jennifer P.; Myrick, Florence T.; Wakefield,
                         Debby A. C. S.; Hooper, Brandi J.; Harris, Jeanette
                         L.; McCreedy, Bruce; Borroto-Esoda, Katyna
CORPORATE SOURCE:        Triangle Pharmaceuticals, Durham, NC, 27707, USA
SOURCE:                  JAIDS, Journal of Acquired Immune Deficiency Syndromes
                         (2002), 29(1), 11-20
                         CODEN: JJASFJ
PUBLISHER:               Lippincott Williams & Wilkins
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Amdoxovir ([-]-β-D-2,6-diaminopurine dioxolane [DAPD]) is a
     nucleoside reverse transcriptase inhibitor (NRTI) with activity against
     HIV-1.  DAPD is deaminated in vivo by adenosine deaminase to
     (-)-β-D-dioxolane guanosine (DXG), a highly active anti-HIV compound
     The median 50% effective concns. (EC50) ± SD (representing antiviral
     activity against a laboratory-derived HIV-1 isolate) for DAPD and DXG in
     peripheral blood mononuclear cells were 4.0±2.2 µmol/L and
     0.25±0.17 µmol/L, resp.  The 50% cytotoxic dose (CC50) of both DAPD
     and DXG was >500 µmol/L.  Recombinant viruses and clin. isolates of
     HIV-1 from patients for whom NRTI therapy and/or nonnucleoside reverse
     transcriptase inhibitor (NNRTI) combination therapies failed
     remained susceptible to inhibition by DXG (less than fourfold change in
     EC50).  Similar anal. showed that recombinant viruses harboring mutations
     known to confer resistance to NRTIs (zidovudine, lamivudine, and abacavir)
     and NNRTIs (efavirenz and nevirapine) as well as the multidrug
     resistance-associated mutation Q151M and double codon insertions
     (SS and SG) were also susceptible to inhibition by DXG.  Resistance to DXG
     was observed only in recombinant isolates containing the 65R and 151M double
     mutations.  Phenotypic anal. of a site-directed mutant containing only the
     151M mutation demonstrated moderate resistance to DXG (<10-fold change in
     EC50).  We also examined site-directed mutants containing only L74V or K65R,
the
     characteristic resistance mutations for DXG.  The L74V mutant remained
     susceptible to inhibition by DXG, and the K65R mutant demonstrated
     moderate resistance to DXG.
TI   Dioxolane guanosine, the active form of the prodrug diaminopurine
     dioxolane, is a potent inhibitor of drug-resistant HIV-1
     isolates from patients for whom standard nucleoside therapy fails
REFERENCE COUNT:         45    THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 13 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2001:103100  CAPLUS
DOCUMENT NUMBER:         135:146879
TITLE:                   Patterns of resistance mutations to antiretroviral
                         drugs in extensively treated HIV-1-infected patients
                         with failure of highly active antiretroviral therapy
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AUTHOR(S):               Rousseau, Marie-Noelle; Vergne, Laurence; Montes,
                         Brigitte; Peeters, Martine; Reynes, Jacques;
                         Delaporte, Eric; Segondy, Michel
CORPORATE SOURCE:        Laboratory of Virology and Department of Infectious
                         and Tropical Diseases, Centre Hospitalier
                         Universitaire (CHU), Montpellier, 34295, Fr.
SOURCE:                  JAIDS, Journal of Acquired Immune Deficiency Syndromes
                         (2001), 26(1), 36-43
                         CODEN: JJASFJ
PUBLISHER:               Lippincott Williams & Wilkins
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Resistance-mutation patterns in the reverse transcriptase (RT) and
     protease genes of HIV-1 were analyzed in 22 patients who had been
     extensively pretreated and who failed to respond to highly active
     antiretroviral therapy (HAART).  The number of mutations ranged from 8 to 19
     (median, 13): 4 to 12 (median, 6) mutations in the RT gene, and 4 to 8
     (median, 7) mutations in the protease gene.  In the RT gene, the most
     frequent resistance mutations were found at codons 215 (100%),
     41 (95%), 67 (91%), and 210 (77%).  Multidrug-resistant mutation
     patterns including Q151M and insertion mutations at codon 69,
     which confer cross-resistance to the different nucleoside analog RT
     inhibitors were detected in 1 and 3 patients, resp.; 1 patient with
     insertion mutation displayed a NGQCV sequence at codons 67 to
     70.  In the protease gene, the most frequent mutations were found at
     codons 63 (95%), 10 (86%), 90(86%), 71(77%), 46 (50%), 36 (45%),
     and 84 (45%).  Genotypic resistance to zidovudine, saquinavir, and
     indinavir was found in 100% of the patients.  All patients showed also
     resistance or possible resistance to stavudine, abacavir, ritonavir, and
     nelfinavir.  Mutations conferring genotypic resistance to nonnucleoside
     analog RT inhibitors (NNRTIs) were found in 12 (80%) of the
     NNRTI-experienced patients and 1 of 7 NNRTI-naive
     patients.  Our results indicate that failure of HAART in the patients
     extensively pretreated results from the multiplicity of RT and protease
     mutations that confer genotypic resistance to almost all available
     antiretroviral drugs.  In these patients, genotypic resistance tests
     confirm the lack of alternative salvage therapy strategies based on the
     currently available antiretroviral drugs.
TI   Patterns of resistance mutations to antiretroviral drugs in extensively
     treated HIV-1-infected patients with failure of highly active
     antiretroviral therapy
REFERENCE COUNT:         26    THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 14 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2000:651756  CAPLUS
DOCUMENT NUMBER:         134:141187
TITLE:                   Non-nucleoside reverse transcriptase inhibitors
AUTHOR(S):               Joly, Veronique; Yeni, Patrick
CORPORATE SOURCE:        Service de Medecine Interne, Hopital Bichat, Paris,
                         75877, Fr.
SOURCE:                  Annales de Medecine Interne (2000), 151(4), 260-267
                         CODEN: AMDIBO; ISSN: 0003-410X
PUBLISHER:               Masson Editeur
DOCUMENT TYPE:           Journal; General Review
LANGUAGE:                French
AB   A review with 64 refs. The non-nucleoside reverse transcriptase inhibitors
     (NNRTIs) directly inhibit the HIV-1 reverse transcriptase (RT)
     by binding to the enzyme in a reversible and noncompetitive manner.  The
     currently available NNRTIs are nevirapine, delavirdine, and
     efavirenz; other compds. are under evaluation.  NNRTIs are
     extensively metabolized in the liver through cytochrome P 450, leading to
     pharmacokinetic interactions with compds. utilizing the same metabolic
     pathway, particularly protease inhibitors, whose plasma levels are altered
     in the presence of NNRTIs.  NNRTIs are drugs with a
     low genetic barrier, i.e., a single mutation in the RT genome induces a
     high level of phenotypic resistance, preventing the use of NNRTIs
     as monotherapy.  In naive patients, several trials have shown the value of
     NNRTIs in combination with nucleosides and/or protease inhibitors.
     Small pilot studies have shown that NNRTIs may be useful as
     2nd-line therapy.  However, due to the rapid emergence of virus
     resistant to these compds. in case of incomplete viral
     suppression, NNRTIs should not be added to current failing
     antiretroviral regimens.  The most common side effect reported with
     nevirapine and delavirdine is rash.  The incidence of rash is rather
     similar with these two compds., but severe rash is less frequent with
     delavirdine.  The most common adverse reactions reported with efavirenz
     are central nervous system complaints such as dizziness.  Rash is reported
     less frequently than with nevirapine or delavirdine, and is usually mild.
     Resistance mutations to NNRTIs are located in the amino acid
     residues at the "pocket" of the NNRTI-binding site.  High-level
     resistance is often associated with a single point mutation which develops
     within this site (especially codon groups 100-108 and 181-190).
     Patients no longer responding to one NNRTI are very likely to
     possess multiple NNRTI resistance mutations.  NNRTIs
     should always be used as part of a potent antiretroviral therapy to insure
     suppression of viral replication, thus circumventing the rapid selection
     of cross-resistant variants.
TI   Non-nucleoside reverse transcriptase inhibitors
REFERENCE COUNT:         64    THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 15 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2000:530225  CAPLUS
DOCUMENT NUMBER:         133:114631
TITLE:                   Prevalence and characteristics of multinucleoside-
                         resistant human immunodeficiency virus type 1
                         among European patients receiving combinations of
                         nucleoside analogues
AUTHOR(S):               Van Vaerenbergh, Kristien; Van Laethem, Kristel;
                         Albert, Jan; Boucher, Charles A. B.; Clotet,
                         Bonaventura; Floridia, Marco; Gerstoft, Jan; Hejdeman,
                         Bo; Nielsen, Claus; Pannecouque, Christophe; Perrin,
                         Luc; Pirillo, Maria F.; Ruiz, Lidia; Schmit,
                         Jean-Claude; Schneider, Francois; Schoolmeester, Anne;
                         Schuurman, Rob; Stellbrink, Hans J.; Stuyver, Lieven;
                         Van Lunzen, Jan; Van Remoortel, Barbara; Van
                         Wijngaerden, Eric; Vella, Stefano; Witvrouw, Myriam;
                         Yerly, Sabine; De Clercq, Erik; Desmyter, Jan;
                         Vandamme, Anne-Mieke
CORPORATE SOURCE:        Rega Institute for Medical Research and University
                         Hospitals, Louvain, B-3000, Belg.
SOURCE:                  Antimicrobial Agents and Chemotherapy (2000), 44(8),
                         2109-2117
                         CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER:               American Society for Microbiology
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The prevalence and the genotypic and phenotypic characteristics of
     multinucleoside-resistant (MNR) human immunodeficiency virus
     type 1 (HIV-1) variants in Europe were investigated in a multicenter study
     that involved centers in nine European countries.  Study samples (n = 363)
     collected between 1991 and 1997 from patients exposed to two or more
     nucleoside analog reverse transcriptase inhibitors (NRTIs) and 274 control
     samples from patients exposed to no or one NRTI were screened for two
     marker mutations of multinucleoside resistance (the Q151M mutation and a
     mutation with a 2-amino-acid insertion at codon 69, T69S-XX).
     Q151M was identified in six of the study samples (1.6%), and T69S-XX was
     identified in two of the study samples (0.5%; both of them T69S-SS), but
     both patterns were absent among control samples.  Non-NRTI (NNRTI
     )-related changes were observed in viral strains from two patients, which
     displayed the Q151M resistance pattern, although the patients were
     NNRTI naive.  The patients whose isolates displayed
     multinucleoside resistance had received treatment with zidovudine and
     either didanosine, zalcitabine, or stavudine.  Both resistance patterns
     conferred broad cross-resistance to NRTIs in vitro and a poor response to
     treatment in vivo.  MNR HIV-1 is found only among multinucleoside-
     experienced patients.  Its prevalence is low in Europe, but it should be
     closely monitored since it seriously limits treatment options.
TI   Prevalence and characteristics of multinucleoside-resistant
     human immunodeficiency virus type 1 among European patients receiving
     combinations of nucleoside analogues
REFERENCE COUNT:         20    THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 16 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2000:191522  CAPLUS
DOCUMENT NUMBER:         132:202697
TITLE:                   Prevalence of HIV-1 resistant to
                         antiretroviral drugs in 81 individuals newly infected
                         by sexual contact or injecting drug use
AUTHOR(S):               Salomon, Horacio; Wainberg, Mark A.; Brenner, Bluma;
                         Quan, Yudong; Rouleau, Danielle; Cote, Pierre;
                         LeBlanc, Roger; Lefebvre, Eric; Spira, Bonnie;
                         Tsoukas, Chris; Sekaly, Rafik-Pierre; Conway, Brian;
                         Mayers, Douglas; Routy, Jean-Pierre
CORPORATE SOURCE:        McGill University AIDS Centre, Montreal, QC, H3T 1E2,
                         Can.
SOURCE:                  AIDS (London) (2000), 14(2), F17-F23
                         CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER:               Lippincott Williams & Wilkins
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Prolonged treatment with antiretroviral drugs results in the selection of
     HIV-1 variants with mutations conferring resistance to nucleoside and
     non-nucleoside reverse transcriptase inhibitors (NRTI and NNRTI)
     or to protease inhibitors (PI).  There is serious concern about
     transmission of resistant viruses to newly infected persons.
     This study monitored the prevalence of resistant viruses in
     individuals undergoing primary HIV infection.  Resistance testing was
     performed on 81 individuals infected between 1997 and 1999 by injecting
     drug use (n = 21), sexual (n = 56), or unknown (n = 4) transmission.
     Automated sequencing was used to genotype the reverse transcriptase (RT)
     and protease regions of virus isolated from patients' plasma.  The
     phenotypic susceptibility of stimulated peripheral blood mononuclear cells
     to antiretroviral drugs was assayed.  Line probe assays detected
     quasispecies variations in wild-type and mutated RT codons.  A
     high prevalence of PI and RT genotypic variants, associated with high-level
     resistance to antiretroviral drugs, was observed in individuals newly
     infected by injecting drug use (PI = 24%, RT = 24%) or sexual transmission
     (PI = 12%, RT = 22%).  The PI mutations, L101, V82A, and L90M, were found
     in 10.5, 3 and 4% of cases, resp.; whereas for RT, primary mutations at
     positions T215Y (zidovudine), M184V (lamivudine), T69D/A (zalcitabine),
     and K103N (multi-NNRTI) were present in 8, 5, 4, and 4% of
     subjects, resp.  Resistance to NRTI was demonstrated by phenotypic,
     genotypic, and line probe analyses.  Transmission of multidrug (NRTI/
     NNRTI/PI) resistance in eight subjects (9.9%) was confirmed by
     showing that source partners possessed viruses of similar genotype.  The
     transmission of drug-resistant HIV is a serious problem that
     merits further attention by public health officials as well as virologists
     and clinicians.
TI   Prevalence of HIV-1 resistant to antiretroviral drugs in 81
     individuals newly infected by sexual contact or injecting drug use
REFERENCE COUNT:         21    THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 17 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        1998:810132  CAPLUS
DOCUMENT NUMBER:         130:162784
TITLE:                   Biochemical characterization of HIV-1 reverse
                         transcriptases encoding mutations at amino acid
                         residues 161 and 208 involved in resistance to
                         phosphonoformate
AUTHOR(S):               Tramontano, Enzo; Piras, Giovanna; Mellors, John W.;
                         Putzolu, Monica; Bazmi, Hengameh Z.; La Colla, Paolo
CORPORATE SOURCE:        Dipartimento di Biologia Sperimentale, Sezione di
                         Microbiologia, Universita di Cagliari, Cagliari,
                         09124, Italy
SOURCE:                  Biochemical Pharmacology (1998), 56(12), 1583-1589
                         CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER:               Elsevier Science Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Mutations at amino acid residues 161 (Q161L) and 208 (H208Y) of the
     reverse transcriptase (RT) have been identified in HIV-1 variants which
     are resistant to phosphonoformate (PFA).  In the present study,
     we report on the biochem. properties of recombinant RTs (rRTs) carrying
     either one or both of the above mutations.  We also report on their
     susceptibility to PFA and to nucleoside (NRTI) and non-nucleoside (
     NNRTI) RT inhibitors.  Like the wild-type (wt) enzyme, mutant rRTs
     H208Y and Q161L/H208Y showed a preference for Mg2+ over Mn2+, whereas the
     Q161L rRT preferred Mn2+.  The three mutant rRTs showed degrees of PFA
     resistance which differed according to the template-primer used, and
     steady-state kinetic studies revealed an inverse correlation between their
     degree of PFA resistance, affinity for deoxynucleoside triphosphates
     (dNTPs) and catalytic efficiency (kcat/Km ratio).  These results indicated
     that HIV-1 rRTs bearing mutations at codons 161 and/or 208 had
     altered dNTP binding sites which led to a PFA-resistant
     phenotype.  However, unlike the corresponding mutant viruses, which are
     hypersensitive to 3'-azido-3'-deoxythymidine (AZT), 11-cyclopropyl-5,-11-
     dihydro-4-methyl-6H-dipyridol[3,2-b:2',3',-e]diazepin-6-one (Nevirapine)
     and (+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-
     imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione, (TIBO R82150), the
     mutant RTs Q161L and Q161L/H208Y were resistant to
     3'-azido-3'-deoxythymidine triphosphate (AZTTP) and as susceptible as the
     wt enzyme to Nevirapine and TIBO R82150.  Overall, these results suggest
     that codons 161 and 208 of the HIV-1 RT gene are involved in
     substrate binding as well as in NRTI recognition, and provide more
     insights into the mechanism by which HIV-1 becomes resistant to
     PFA.
TI   Biochemical characterization of HIV-1 reverse transcriptases encoding
     mutations at amino acid residues 161 and 208 involved in resistance to
     phosphonoformate
REFERENCE COUNT:         27    THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 18 OF 34  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        1996:37786  CAPLUS
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DOCUMENT NUMBER: 124:134873
TITLE: Selective pressure of a quinoxaline nonnucleoside inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) on HIV-1 replication results in the emergence of nucleoside RT-inhibitor-specific (RT Leu-74 → Val or Ile and Val-75 → Leu or Ile) HIV-1 mutants
AUTHOR(S): Kleim, Joerg-Peter; Roesner, Manfred; Winkler, Irwin; Paessens, Arno; Kirsch, Reinhard; Hsiou, Yu; Arnold, Edward; Riess, Guenther
CORPORATE SOURCE: Hoechst AG, General Pharma Res., Frankfurt, D-65926, Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1996), 93(1), 34-8
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The quinoxaline nonnucleoside RT inhibitor (NNRTI) (S)-4-isopropoxycarbonyl-6-methoxy-3-(methylthiomethyl)-3,4-dihydroquinoxaline-2(1H)-thione (HBT 097) was used to select for drug-resistant HIV-1 variants in vitro. The viruses first developed mutations affecting the NNRTI-binding pocket, and five of six strains displayed the RT G190→E substitution, which is characteristic for HIV-1 resistance against quinoxalines. In one variant, a new mutant (G190→Q) most likely evolved from preexisting G190→E mutants. The neg. charge introduced by the G190→E substitution was maintained at the site of the pocket by simultaneous selection for V179→D together with G190→Q. After continued exposure to the drug, mutations at positions so far known to be specific for resistance against nucleoside RT inhibitors (NRTIs) (L74→V/I and V75→L/I) were consistently detected in all cultures. The inhibitory activities of the cellular conversion product of 2',3'-dideoxyinosine (ddI, didanosine), 2',3'-dideoxyadenosine (ddA) and of 2',3'-didehydro-3'-deoxythymidine (d4T, stavudine) against these late-passage viruses were shown to be enhanced with the L74→V/I RT mutant virus as compared with the wild-type (wt HIV-1MN isolate). Clonal anal. proved linkage of the codon 74 and codon 75 mutations to the NNRTI-specific mutations in all RT gene fragments. The nonnucleoside- and nucleoside-resistance mutation sites are separated by approx. 35 Å. We propose that the two sites "communicate" through the template-primer which is situated in the DNA-binding cleft between these two sites. Quinoxalines cause high selective pressure on HIV-1 replication in vitro; however, the implication of these findings for the treatment of HIV-1 infection has yet to be determined

TI Selective pressure of a quinoxaline nonnucleoside inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) on HIV-1 replication results in the emergence of nucleoside RT-inhibitor-specific (RT Leu-74 → Val or Ile and Val-75 → Leu or Ile) HIV-1 mutants

L5 ANSWER 19 OF 34 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:160552 BIOSIS
DOCUMENT NUMBER: PREV200700163933
TITLE: Genotype and phenotype patterns of drug-resistant HIV-1 subtype B ' (Thai B) isolated from patients failing antiretroviral therapy in China.
AUTHOR(S): Ma, Liying; Sun, Jianping; Xing, Hi; Si, Xefeng; Yuan, Lin; Guo, Yanfang; Cheng, Hua; Shao, Yiming [Reprint Author]
CORPORATE SOURCE: Chinese Ctr Dis Control and Prevent, Natl Ctr AIDS STD Control and Prevent, State Key Lab Infect Dis Prevent and

Control, Beijing 100050, Peoples R China
yshao@bbn.cn
SOURCE: JAIDS Journal of Acquired Immune Deficiency Syndromes, (JAN 1 2007) Vol. 44, No. 1, pp. 14-19.
ISSN: 1525-4135.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Mar 2007
Last Updated on STN: 7 Mar 2007

AB Many AIDS patients in China who received free-of-charge antiretroviral therapeutics, including nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), showed significant life improvement. Increasing numbers of patients, however, are experiencing antiretroviral therapy failure due to the emergence of drug-resistant viruses. The aim of this study was to investigate the genotypic and phenotypic drug resistance patterns of HIV-1 subtype B' variants, which are prevalent in China, in order to rationally design more efficient anti-HIV-1 regimens for future treatment of AIDS patients. 13 out of 16 patients (81%) who were treated with two NRTIs (ddI, and d4T or AZT) and one NNRTI (NVP) exhibited high resistance to NVP, 8 of them with a > 1,000 IC50 fold increase. Five codons (10 1, 103, 108, 181, and 190) were involved in the NVP-resistant mutations, and K103N and Y181C mutations were predominant in these isolates. Fifteen isolates were resistant to at least one of the NRTIs, with high resistance to AZT (> 10 IC50 fold increase) and intermediate resistance to d4T or ddI (similar to 4 IC50 fold increase). More than 10 codons were involved in the NRTI-resistant mutation and located in two regions (M41-V75 and T215-K219) of the reverse transcriptase. Concordance between the genotype and phenotype patterns for both NRTIs and NNRTI were detected in a majority of the isolates, suggesting that phenotypic resistance is predictable from genotyping assays, which are faster and less expensive than phenotypic assay. Because NVP and AZT can induce high resistances in these patients, these two drugs should be replaced with others more effective NNRTIs and NRTIs.

TI Genotype and phenotype patterns of drug-resistant HIV-1 subtype B ' (Thai B) isolated from patients failing antiretroviral therapy in China.

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ACCESSION NUMBER: 2006:334230 BIOSIS
DOCUMENT NUMBER: PREV200600325675
TITLE: Selection and persistence of non-nucleoside reverse transcriptase inhibitor-resistant HIV-1 in patients starting and stopping non-nucleoside therapy.
AUTHOR(S): Palmer, Sarah [Reprint Author]; Boltz, Valerie; Maldarelli, Frank; Kearney, Mary; Halvas, Elias K.; Rock, Diane; Falloon, Judith; Davey, Richard T. Jr; Dewar, Robin L.; Metcalf, Julia A.; Mellors, John W.; Coffin, John A
CORPORATE SOURCE: NCI, HIV Drug Resistance Program, NIH, 1050 Boyles St,Bldg 535,Room 109, Frederick, MD 21702 USA
spalmer@ncifcrf.gov
SOURCE: AIDS (Hagerstown), (MAR 21 2006) Vol. 20, No. 5, pp. 701-710.
CODEN: AIDSET. ISSN: 0269-9370.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Jun 2006
Last Updated on STN: 28 Jun 2006

AB Background: Understanding the selection and decay of drug-resistant HIV-1 variants is important for designing optimal antiretroviral therapy.Objective: To develop a high-throughput, real-time reverse transcriptase (RT) polymerase chain reaction (PCR) assay to quantify non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant variants K103N (AAT or AAC alleles) at frequencies as low as 0.1%, and to apply this to monitor these variants before, during, and after NNRTI therapy.Methods: HIV-1 RNA in longitudinal plasma samples obtained from patients starting and stopping NNRTI therapy was converted to cDNA and the target sequence region amplified and quantified by real-time PCR. Approximately 10(7) copies/reaction provided a template for a second round of PCR using primers that discriminated between the mutant and wild-type alleles. Amplification specificity was confirmed by thermal denaturation analysis.Results: Frequencies of 103N similar to assay background (0.029%) were observed in longitudinal samples from 9 of 12 treatment-naive patients; three patients had transient increases in 103N frequency to a range of 0.21-0.48%, which was 7-16.5 times assay background. Analysis of longitudinal plasma samples from six NNRTI-experienced patients showed three patterns: persistence of 103N variants after stopping NNRTI therapy, codon switching of 103N between AAC and AAT during NNRTI therapy, and decay of 103N variants to below assay background after cessation of NNRTI therapy.Conclusions: Allele-specific RT-PCR quantified the emergence and decay of drug-resistant variants in patients over a broad range of frequencies (0.1-100%). The rate of decay of K103N variants after stopping NNRTI therapy was highly variable. (C) 2006 Lippincott Williams & Wilkins.

TI Selection and persistence of non-nucleoside reverse transcriptase inhibitor-resistant HIV-1 in patients starting and stopping non-nucleoside therapy.

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ACCESSION NUMBER: 2006:232157 BIOSIS
DOCUMENT NUMBER: PREV200600235146
TITLE: Mutations other than 103N in human immunodeficiency virus type 1 reverse transcriptase (RT) emerge from K103R polymorphism under non-nucleoside RT inhibitor pressure.
AUTHOR(S): Gatanaga, Hiroyuki [Reprint Author]; Hachiya, Atsuko; Kimura, Satoshi; Oka, Shinichi
CORPORATE SOURCE: Int Med Ctr Japan, AIDS Clin Ctr, Shinjuku Ku, 1-21-1 Toyama, Tokyo 1628655, Japan higatana@imcj.acc.go.jp
SOURCE: Virology, (JAN 20 2006) Vol. 344, No. 2, pp. 354-362. CODEN: VIRLAX. ISSN: 0042-6822.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Apr 2006
Last Updated on STN: 12 Apr 2006

AB K103N mutation in human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) confers high-level resistance against non-nucleoside RT inhibitors (NNRTIs) and it easily occurs partly because it arises by a single nucleotide substitution from wild-type K103. There are polymorphisms at codon 103 of HIV-1 RT. We found K103R polymorphic mutation in 3.3% of treatment-naive HIV-1-infected patients. R103N does not seem to occur as easily as K103N because R103N requires two nucleotide substitutions. To induce NNRTI resistance-associated mutations, HIV-1(K103R) was propagated in the presence of increasing concentrations of efavirez (EFV) or nevirapine (NVP). V1791) emerged in all three EFV cultures and in two of four NVP cultures. R103G emerged by a single nucleotide substitution in one of three EFV cultures. R103N did not emerge in any of 7 NNRTI cultures. Analysis of recombinant HIV-1s showed that HIV-1(K103R/V179D) was significantly resistant and HIV-1(K103G) was moderately resistant against EFV and NVP.

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     (C) 2005 Elsevier Inc.  All rights reserved.
TI   Mutations other than 103N in human immunodeficiency virus type 1 reverse
     transcriptase (RT) emerge from K103R polymorphism under non-nucleoside RT
     inhibitor pressure.

L5   ANSWER 22 OF 34  BIOSIS  COPYRIGHT (c) 2008 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2006:176984  BIOSIS
DOCUMENT NUMBER:     PREV200600160375
TITLE:               Prevalence and evolution of drug resistance HIV-1 variants
                     in Henan, China.
AUTHOR(S):           Li, Jing Yun [Reprint Author]; Li, Han Ping; Li, Lin; Li,
                     Hong; Wang, Zhe; Yang, Kun; Bao, Zuo Yi; Zhuang, Dao Min;
                     Liu, Si Yang; Liu, Yong Jian; Xing, Hui; Shao, Yi Ming
CORPORATE SOURCE:    Acad Mil Med Sci, Inst Microbiol and Epidemiol, AIDS Res
                     Dept, Beijing 100071, Peoples R China
                     lijy@nic.bmi.ac.cn
SOURCE:              Cell Research, (NOV-DEC 2005) Vol. 15, No. 11-12, pp.
                     843-849.
                     ISSN: 1001-0602.
DOCUMENT TYPE:       Article
LANGUAGE:            English
ENTRY DATE:          Entered STN: 9 Mar 2006
                     Last Updated on STN: 9 Mar 2006
AB   To understand the prevalence and evolution of drug resistant HIV
     strains in Henan China after the implementation of free antiretroviral
     therapy for AIDS patients. 45 drug naive AIDS patients, 118 AIDS patients
     who received three months antiretroviral therapy and 124 AIDS patients who
     received six months antiretroviral treatment were recruited in the
     southern part of Henan province.  Information on general condition,
     antiretroviral medicines, adherence and clinical syndromes were collected
     by face to face interview.  Meanwhile, 14ml EDTA anticoagulant blood was
     drawn.  CD4/CD8 T cell count, viral load and genotypic drug resistance
     were tested.  The rates of clinical improvement were 55.1% and 50.8%
     respectively three months and six months after antiretroviral therapy.
     The mean CD4 cell count after antiretroviral therapy was significantly
     higher than in drug naive patients.  The prevalence rate of drug
     resistant HIV strains were 13. 9%, 45.4% and 62.7% in drug naive
     patients, three month treatment patients and six month treatment patients,
     respectively.  The number of resistance mutation codons and the
     frequency of mutations increased significantly with continued
     antiretroviral therapy.  The mutation sites were primarily at the 103, 106
     and 215 codons in the three-month treatment group and they
     increased to 15 codon mutations in the six-month treatment
     group.  From this result, the evolution of drug resistant
     strains was inferred to begin with the high level NNRTI
     resistant strain, and then develop low level resistant
     strains to NRTIs.  The HIV strains with high level resistance to NVP and
     low level resistance to AZT and DDI were highly prevalent because of the
     AZT+DDI+NVP combination therapy.  These HIV strains were also cross
     resistant to DLV, EFV, DDC and D4T.  Poor adherence to therapy was
     believed to be the main reason for the emergence and prevalence of drug
     resistant HIV strains.  The prevalence of drug resistant
     HIV strains was increased with the continuation of antiretroviral therapy
     in the southern part of Henan province.  Measures, that could promote high
     level adherence, provide new drugs and change ART regimens in failing
     patients, should be implemented as soon as possible.
TI   Prevalence and evolution of drug resistance HIV-1 variants in Henan,
     China.

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ACCESSION NUMBER:    2005:495218  BIOSIS
DOCUMENT NUMBER:     PREV200510285357
TITLE:               The role of Thr139 in the human immunodeficiency virus type
                     1 reverse transcriptase sensitivity to (+)-calanolide A.
AUTHOR(S):           Auwerx, Joeri; Rodriguez-Barrios, Fatima;
                     Ceccherini-Silberstein, Francesca; San-Felix, Ana;
                     Velazquez, Sonsoles; De Clercq, Erik; Camarasa, Maria-Jose;
                     Perno, Carlo-Federico; Gago, Federico; Balzarini, Jan
                     [Reprint Author]
CORPORATE SOURCE:    Catholic Univ Louvain, Rega Inst Med Res, Minderbroedersstr
                     10, B-3000 Louvain, Belgium
                     jan.balzarini@rega.kuleuven.be
SOURCE:              Molecular Pharmacology, (SEP 2005) Vol. 68, No. 3, pp.
                     652-659. http:/www.molpharm.org.
                     CODEN: MOPMA3. ISSN: 0026-895X.
DOCUMENT TYPE:       Article
LANGUAGE:            English
ENTRY DATE:          Entered STN: 16 Nov 2005
                     Last Updated on STN: 16 Nov 2005
AB   The coumarins represent a unique class of non-nucleoside reverse
     transcriptase inhibitors (NNRTIs) that were isolated from
     tropical plants. (+)-Calanolide A, the most potent compound of this class,
     selects for the T139I resistance mutation in HIV-1 reverse transcriptase
     (RT).  Seven RTs mutated at amino acid position 139 (Ala, Lys, Tyr, Asp,
     Ile, Ser, and Gln) were constructed by site-directed mutagenesis.  The
     mutant T139Q enzyme retained full catalytic activity compared with
     wild-type RT, whereas the mutant T139I, T139S, and T139A RTs retained only
     85 to 50% of the activity.  Mutant T139K, T139D, and T139Y RTs had
     seriously impaired catalytic activities.  The mutations in the T139I and
     T139D RTs were shown to destabilize the RT heterodimer. (+)-Calanolide A
     lost inhibitory activity (up to 20-fold) against the mutant T139Y, T139Q,
     T139K, and T139I enzymes.  All of the mutant enzymes retained marked
     susceptibility toward the other NNRTIs, including nevirapine,
     delavirdine, efavirenz, thiocarboxanilide UC-781, quinoxaline GW867420X,
     TSAO [[2',5'-bis-O-(tert-butyldimethylsilyl)-beta-D-ribofuranosyl]-3'-
     spiro-5 ''-(4 ''-amino-1 '',2 ''-oxathiole-2 '',2 ''-dioxide)]derivatives,
     and the nucleoside inhibitor, ddGTP.  The fact that the T139I RT 1) proved
     to be resistant to (+)-calanolide A, 2) represents a
     catalytically efficient enzyme, and 3) requires only a single transition
     point mutation (ACA -> ATA) in codon 139 seems to explain why
     mutant T139I RT virus strains, but not virus strains containing other
     amino acid changes at this position, predominantly emerge in cell cultures
     under (+)-calanolide A pressure.
TI   The role of Thr139 in the human immunodeficiency virus type 1 reverse
     transcriptase sensitivity to (+)-calanolide A.

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     STN
ACCESSION NUMBER:    2004:68760  BIOSIS
DOCUMENT NUMBER:     PREV200400060800
TITLE:               Evolution of human immunodeficiency virus type 1 (HIV-1)
                     resistance mutations in nonnucleoside reverse transcriptase
                     inhibitors (NNRTIs) in HIV-1-infected patients
                     switched to antiretroviral therapy without NNRTIs
                     .
AUTHOR(S):           Joly, Veronique [Reprint Author]; Descamps, Diane;
                     Peytavin, Gilles; Touati, Fatiha; Mentre, France; Duval,
                     Xavier; Delarue, Severine; Yeni, Patrick; Brun-Vezinet,
                     Francoise
CORPORATE SOURCE:    Hopital Bichat Claude Bernard, 46 Rue Henri Huchard, 75877,
                     Paris Cedex, 18, France
                     veronique.joly@bch.ap-hop-paris.fr
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SOURCE: Antimicrobial Agents and Chemotherapy, (January 2004) Vol. 48, No. 1, pp. 172-175. print.
ISSN: 0066-4804 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Jan 2004
Last Updated on STN: 28 Jan 2004

AB We studied the evolution of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations among 29 human immunodeficiency virus type 1 (HIV-1)-infected patients who experienced virologic failure when receiving an NNRTI-containing regimen (nevirapine, delavirdine, or efavirenz) and subsequently switched to antiretroviral therapy without NNRTIs. Genotypic resistance was determined from plasma samples collected at the time of NNRTI withdrawal (baseline) and during follow-up. At baseline, 83% of patients had more than two thymidine analog resistance mutations (TAMs), and all had NNRTI resistance mutations. Mutations at codons 103, 181, and 190 were found in 62, 62, and 34% of the patients, respectively. Follow-up samples were available after a median time of 6 months in all patients and at 12 months in 22 patients. The mean number of resistance mutations to NNRTIs was significantly lower at months 6 (1.34 +- 1.04) and 12 (1.18 +- 1.05) than at month 0 (2.03 +- 1.02) (P < 0.009). The percentages of patients with at least one NNRTI resistance mutation were 100, 76, and 73% at baseline, month 6, and month 12, respectively (P < 0.0044). Overall, 70% of the patients had a mutation at codon 103 or 181 at month 12. The mean number of TAMs did not vary significantly during follow-up. Our data show that, in the context of maintained antiretroviral therapy, NNRTI resistance mutations persist in two-thirds of the patients in spite of NNRTI withdrawal. These results argue for the low impact of NNRTI resistance mutations on viral fitness and suggest that resistance mutations to different classes of drugs are associated on the same genome, at least in some of the resistant strains.

TI Evolution of human immunodeficiency virus type 1 (HIV-1) resistance mutations in nonnucleoside reverse transcriptase inhibitors (NNRTIs) in HIV-1-infected patients switched to antiretroviral therapy without NNRTIs.

L5 ANSWER 25 OF 34 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:10338 BIOSIS
DOCUMENT NUMBER: PREV200400014732
TITLE: Drug resistance profiles of recombinant reverse transcriptases from human immunodeficiency virus type 1 subtypes A/E, B, and C.
AUTHOR(S): Quan, Yudong; Brenner, Bluma G.; Marlink, Richard G.; Essex, Max; Kurimura, Takashi; Wainberg, Mark A. [Reprint Author]
CORPORATE SOURCE: Jewish General Hospital, Lady Davis Institute, 3755 Chemin de la Cote Ste-Catherine, Montreal, PQ, H3T 1E2, Canada
mark.wainberg@mcgill.ca
SOURCE: AIDS Research and Human Retroviruses, (September 2003) Vol. 19, No. 9, pp. 743-753. print.
ISSN: 0889-2229 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003

AB We have expressed purified recombinant reverse transcriptase (RT) from clinical isolates of human immunodeficiency virus subtypes B, C, and A/E in Escherichia coli. The drug sensitivities of these RTs were then determined for both nucleoside RT inhibitors (NRTIs) and nonnucleoside RT inhibitors (NNRTIs) in cell-free RT assays. Although A/E and C viruses contained numerous polymorphisms relative to subtype B (i.e., naturally occurring variations unrelated to drug resistance), the wild-type enzymes prepared from these or subtype A/E clinical isolates displayed <2-fold differences in drug sensitivities with regard to the active triphosphate active forms of NRTIs, as compared with RT expressed from BH-10 recombinant virus. Recombinant RTs from clinical isolates of subtypes B, C, and A/E that contained multiple resistance-associated mutations displayed expected variations in levels of resistance to the intracellular active forms of 3TC, ddI, ddC, and PMPA, that is, 3TCTP, ddATP, ddCTP, and PMPApp, respectively. Subtype A/E and C RT enzymes contained only minor NNRTI polymorphisms that distinguished them from wild-type subtype B enzymes and wild-type RTs from these various subtypes showed only 1- to 4-fold variability in IC50 values for each of nevirapine (NVP), delavirdine (DLV), efavirenz (EFV), and calanolide A. In contrast, RT enzymes from subtype B and C viruses harboring specific NNRTI mutations were highly resistant to all four tested NNRTIs. Subtype C variants containing the novel V106M resistance codon showed cross-resistance to all approved NNRTIs in cell-free RT assays.

TI Drug resistance profiles of recombinant reverse transcriptases from human immunodeficiency virus type 1 subtypes A/E, B, and C.

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ACCESSION NUMBER: 2003:565439 BIOSIS
DOCUMENT NUMBER: PREV200300567008
TITLE: Human immunodeficiency virus type 1: Drug resistance in treated and untreated Brazilian children.
AUTHOR(S): Simonetti, S. R. R. [Reprint Author]; Schatzmayr, H. G.; Simonetti, J. P.
CORPORATE SOURCE: Nucleo de Retrovirus, Departamento de Virologia, Instituto Oswaldo Cruz-Fiocruz, Av. Brasil 4365, 21045-900, Rio de Janeiro, RJ, Brazil
ssimonet@ioc.fiocruz.br
SOURCE: Memorias do Instituto Oswaldo Cruz, (September 2003) Vol. 98, No. 6, pp. 831-837. print.
ISSN: 0074-0276 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 2003
Last Updated on STN: 3 Dec 2003

AB Twenty-two vertically human immunodeficiency virus type 1 (HIV-1) infected Brazilian children were studied for antiretroviral drug resistance. They were separated into 2 groups according to the administration of antiretroviral therapy into those who presented disease symptoms or without symptoms and no therapy. Viral genome sequencing reactions were loaded on an automated DNA sampler (TruGene, Visible Genetics) and compared to a database of wild type HIV-1. In the former group 8 of 12 children presented isolates with mutations conferring resistance to protease inhibitors (PIs), 7 presented isolates resistant to nucleoside reverse transcriptase inhibitors (NRTIs) and 2 presented isolates resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs). Ten children were included in the antiretroviral naive group. Eight were susceptible to NRTIs and all of them were susceptible to PIs; one presented the V108I mutation, which confers low-level resistance to NNRTIs. The data report HIV mutant isolates both in treated and untreated infants. However, the frequency and the level of drug resistance were more frequent in the group receiving antiretroviral therapy, corroborating the concept of selective pressure acting on the emergence of resistant viral strains.
The children who presented alterations at polymorphism sites should be

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     monitored for the development of additional mutations occurring at
     relevant resistance codons.
TI   Human immunodeficiency virus type 1: Drug resistance in treated and
     untreated Brazilian children.

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     STN
ACCESSION NUMBER:    2002:339104  BIOSIS
DOCUMENT NUMBER:     PREV200200339104
TITLE:               Mutations associated with genotypic resistance to
                     antiretroviral therapy in treatment naive HIV-1 infected
                     patients in Greece.
AUTHOR(S):           Magiorkinis, E.; Paraskevis, D.; Magiorkinis, G.; Chryssou,
                     S.; Chini, M.; Lazanas, M.; Paparizos, V.; Saroglou, G.;
                     Antoniadou, A.; Giamarellou, E.; Karafoulidou, A.;
                     Hatzakis, A. [Reprint author]
CORPORATE SOURCE:    Department of Hygiene and Epidemiology, National Retrovirus
                     Reference Center, Athens School of Medicine, University of
                     Athens, Alexanfroupoles 25, GR-115 27, Athens, Greece
                     ahatzak@cc.uoa.gr
SOURCE:              Virus Research, (23 April, 2002) Vol. 85, No. 1, pp.
                     109-115. print.
                     CODEN: VIREDF. ISSN: 0168-1702.
DOCUMENT TYPE:       Article
LANGUAGE:            English
ENTRY DATE:          Entered STN: 12 Jun 2002
                     Last Updated on STN: 12 Jun 2002
AB   The widespread use of antiviral drugs against HIV has increased the
     prevalence of HIV-1 resistant strains among naive individuals
     due to transmission of resistant strains.  The purpose of this
     study was to investigate the presence of HIV-1 strains harboring
     resistance mutations in naive patients in Greece.  Blood samples were
     collected from 25 individuals.  The DNA sequence of protease and partial
     reverse transcriptase regions (codons 41-223) were obtained by
     direct sequencing.  Our results showed the absence of any primary
     resistance mutations in the study population.  However, we were able to
     identify high prevalence of sequence polymorphisms at positions in reverse
     transcriptase region associated mainly with resistance to NNRTIs
     .  Moreover, in protease region several secondary mutations were detected,
     suggesting the higher genetic variability of this region.  The clinical
     significance of the polymorphisms associated with reduced susceptibility
     to NNRTIs remains to be clarified.
TI   Mutations associated with genotypic resistance to antiretroviral therapy
     in treatment naive HIV-1 infected patients in Greece.

L5   ANSWER 28 OF 34  BIOSIS  COPYRIGHT (c) 2008 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2002:167386  BIOSIS
DOCUMENT NUMBER:     PREV200200167386
TITLE:               Dioxolane guanosine, the active form of the prodrug
                     diaminopurine dioxolane, is a potent inhibitor of drug-
                     resistant HIV-1 isolates from patients for whom
                     standard nucleoside therapy fails.
AUTHOR(S):           Mewshaw, Jennifer P.; Myrick, Florence T.; Wakefield, Debby
                     A. C. S.; Hooper, Brandi J.; Harris, Jeanette L.; McCreedy,
                     Bruce; Borroto-Esoda, Katyna [Reprint author]
CORPORATE SOURCE:    Triangle Pharmaceuticals, 4 University Place, 4611
                     University Drive, Durham, NC, 27707, USA
                     borrotke@tripharm.com
SOURCE:              JAIDS Journal of Acquired Immune Deficiency Syndromes,
                     (January 1, 2002) Vol. 29, No. 1, pp. 11-20. print.
                     ISSN: 1525-4135.
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DOCUMENT TYPE:      Article
LANGUAGE:           English
ENTRY DATE:         Entered STN: 5 Mar 2002
                    Last Updated on STN: 4 Apr 2002
AB   Amdoxovir ((-)-beta-D-2,6-diaminopurine dioxolane (DAPD)) is a nucleoside
     reverse transcriptase inhibitor (NRTI) with activity against HIV-1.  DAPD
     is deaminated in vivo by adenosine deaminase to (-)-beta-D-dioxolane
     guanosine (DXG), a highly active anti-HIV compound.  The median 50%
     effective concentrations (EC50)+-SD (representing antiviral activity
     against a laboratory-derived HIV-1 isolate) for DAPD and DXG in peripheral
     blood mononuclear cells were 4.0+-2.2 mumol/L and 0.25+-0.17 mumol/L,
     respectively.  The 50% cytotoxic dose (CC50) of both DAPD and DXG was >500
     mumol/L.  Recombinant viruses and clinical isolates of HIV-1 from patients
     for whom NRTI therapy and/or nonnucleoside reverse transcriptase inhibitor
     (NNRTI) combination therapies failed remained susceptible to
     inhibition by DXG (less than fourfold change in EC50).  Similar analysis
     showed that recombinant viruses harboring mutations known to confer
     resistance to NRTIs (zidovudine, lamivudine, and abacavir) and
     NNRTIs (efavirenz and nevirapine) as well as the multidrug
     resistance-associated mutation Q151M and double codon insertions
     (SS and SG) were also susceptible to inhibition by DXG.  Resistance to DXG
     was observed only in recombinant isolates containing the 65R and 151M
     double mutations.  Phenotypic analysis of a site-directed mutant
     containing only the 151M mutation demonstrated moderate resistance to DXG
     (<10-fold change in EC50).  We also examined site-directed mutants
     containing only L74V or K65R, the characteristic resistance mutations for
     DXG.  The L74V mutant remained susceptible to inhibition by DXG, and the
     K65R mutant demonstrated moderate resistance to DXG.
TI   Dioxolane guanosine, the active form of the prodrug diaminopurine
     dioxolane, is a potent inhibitor of drug-resistant HIV-1
     isolates from patients for whom standard nucleoside therapy fails.

L5   ANSWER 29 OF 34  BIOSIS  COPYRIGHT (c) 2008 The Thomson Corporation  on
     STN
ACCESSION NUMBER:   2001:170203  BIOSIS
DOCUMENT NUMBER:    PREV200100170203
TITLE:              Non-nucleosidic reverse transcriptase inhibitors.
                    Original Title: Inhibiteurs non nucleosidiques de la
                    transcriptase inverse.
AUTHOR(S):          Joly, Veronique [Reprint author]; Yeni, Patrick
CORPORATE SOURCE:   Service de Medecine Interne, Hopital Bichat, 75877, Paris
                    Cedex 18, France
SOURCE:             Annales de Medecine Interne, (Juin, 2000) Vol. 151, No. 4,
                    pp. 260-267. print.
                    CODEN: AMDIBO. ISSN: 0003-410X.
DOCUMENT TYPE:      Article
LANGUAGE:           French
ENTRY DATE:         Entered STN: 4 Apr 2001
                    Last Updated on STN: 18 Feb 2002
AB   The non-nucleoside reverse transcriptase inhibitors (NNRTIs)
     directly inhibit the HIV-1 reverse transcriptase (RT) by binding in a
     reversible and non-competitive manner to the enzyme.  The currently
     available NNRTIs are nevirapine, delavirdine, and efavirenz;
     other compounds are under evaluation.  NNRTIs are extensively
     metabolized in the liver through cytochrome P450, leading to
     pharmacokinetic interactions with compounds utilizing the same metabolic
     pathway, particularly PIs, whose plasma levels are altered in the presence
     of NNRTIs.  NNRTIs are drugs with a low genetic
     barrier, i.e. a single mutation in RT genoma induces a high-level of
     phenotypic resistance, preventing the use of NNRTIs as
     monotherapy.  In naive patients, several trials have shown the value of
     NNRTIs in combination with nucleosides and/or protease inhibitors.
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Small pilot studies have shown that NNRTIs may be useful as second-line therapy. However, due to the rapid emergence of resistant virus to these compounds in case of incomplete viral suppression, NNRTIs should not be added to current failing antiretroviral regimen. The most common side-effect reported with nevirapine and delavirdine is rash. The incidence of rash is rather similar under these two compounds, but severe rash is less frequent with delavirdine. The most common adverse reactions reported with efavirenz are central nervous system complaints such as dizziness. Rash is reported less frequently than with nevirapine or delavirdine, and is usually mild. NNRTIs resistance mutations are located in the aminoacid residues aligning the NNRTI-binding "pocket" site. High-level resistance is often associated with a single point mutation which develops within this site (especially codon groups 100 - 108 and 181 - 190). Patients failing on one NNRTI are very likely to possess multiple NNRTI resistance mutations. NNRTIs should always be used as part of a potent antiretroviral therapy to insure suppression of viral replication, thus circumventing the rapid selection of cross-resistant variants.

TI Non-nucleosidic reverse transcriptase inhibitors.
Original Title: Inhibiteurs non nucleosidiques de la transcriptase inverse.

L5 ANSWER 30 OF 34 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:136415 BIOSIS
DOCUMENT NUMBER: PREV200100136415
TITLE: Patterns of resistance mutations to antiretroviral drugs in extensively treated HIV-1-infected patients with failure of highly active antiretroviral therapy.
AUTHOR(S): Rousseau, Marie-Noelle; Vergne, Laurence; Montes, Brigitte; Peeters, Martine; Reynes, Jacques; Delaporte, Eric; Segondy, Michel [Reprint author]
CORPORATE SOURCE: Laboratoire de Virologie, Hopital Saint-Eloi, 80 Avenue Augustin Fliche, 34295, Montpellier Cedex 05, France
m-segondy@chu-montpellier.fr
SOURCE: JAIDS Journal of Acquired Immune Deficiency Syndromes, (January 1, 2001) Vol. 26, No. 1, pp. 36-43. print.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Mar 2001
Last Updated on STN: 15 Feb 2002

AB Resistance-mutation patterns in the reverse transcriptase (RT) and protease genes of HIV-1 were analyzed in 22 patients who had been extensively pretreated and who failed to respond to highly active antiretroviral therapy (HAART). The number of mutations ranged from 8 to 19 (median, 13): 4 to 12 (median, 6) mutations in the RT gene, and 4 to 8 (median, 7) mutations in the protease gene. In the RT gene, the most frequent resistance mutations were found at codons 215 (100%), 41 (95%), 67 (91%), and 210 (77%). Multidrug-resistant mutation patterns including Q151M and insertion mutations at codon 69, which confer cross-resistance to the different nucleoside analogue RT inhibitors were detected in 1 and 3 patients, respectively; 1 patient with insertion mutation displayed a NGQCV sequence at codons 67 to 70. In the protease gene, the most frequent mutations were found at codons 63 (95%), 10 (86%), 90(86%), 71(77%), 46 (50%), 36 (45%), and 84 (45%). Genotypic resistance to zidovudine, saquinavir, and indinavir was found in 100% of the patients. All patients showed also resistance or possible resistance to stavudine, abacavir, ritonavir, and nelfinavir. Mutations conferring genotypic resistance to nonnucleoside analogue RT inhibitors (NNRTIs) were found in 12 (80%) of the NNRTI-experienced patients and 1 of 7 NNRTI-naive patients. Our results indicate that failure of HAART in the patients extensively pretreated results from the multiplicity of RT and protease mutations that confer genotypic resistance to almost all available antiretroviral drugs. In these patients, genotypic resistance tests confirm the lack of alternative salvage therapy strategies based on the currently available antiretroviral drugs.

TI Patterns of resistance mutations to antiretroviral drugs in extensively treated HIV-1-infected patients with failure of highly active antiretroviral therapy.

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ACCESSION NUMBER: 2000:378774 BIOSIS
DOCUMENT NUMBER: PREV200000378774
TITLE: Prevalence and characteristics of multinucleoside-resistant human immunodeficiency virus type 1 among European patients receiving combinations of nucleoside analogues.
AUTHOR(S): Van Vaerenbergh, Kristien [Reprint author]; Van Laethem, Kristel; Albert, Jan; Boucher, Charles A. B.; Clotet, Bonaventura; Floridia, Marco; Gerstoft, Jan; Hejdeman, Bo; Nielsen, Claus; Pannecouque, Christophe; Perrin, Luc; Pirillo, Maria F.; Ruiz, Lidia; Schmit, Jean-Claude; Schneider, Francois; Schoolmeester, Anne; Schuurman, Rob; Stellbrink, Hans J.; Stuyver, Lieven; Van Lunzen, Jan; Van Remoortel, Barbara; Van Wijngaerden, Eric; Vella, Stefano; Witvrouw, Myriam; Yerly, Sabine; De Clercq, Erik; Desmyter, Jan; Vandamme, Anne-Mieke
CORPORATE SOURCE: Rega Institute for Medical Research and University Hospitals, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000, Leuven, Belgium
SOURCE: Antimicrobial Agents and Chemotherapy, (August, 2000) Vol. 44, No. 8, pp. 2109-2117. print.
CODEN: AMACCQ. ISSN: 0066-4804.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Sep 2000
Last Updated on STN: 8 Jan 2002

AB The prevalence and the genotypic and phenotypic characteristics of multinucleoside-resistant (MNR) human immunodeficiency virus type 1 (HIV-1) variants in Europe were investigated in a multicenter study that involved centers in nine European countries. Study samples (n = 363) collected between 1991 and 1997 from patients exposed to two or more nucleoside analogue reverse transcriptase inhibitors (NRTIs) and 274 control samples from patients exposed to no or one NRTI were screened for two marker mutations of multinucleoside resistance (the Q151M mutation and a mutation with a 2-amino-acid insertion at codon 69, T69S-XX). Q151M was identified in six of the study samples (1.6%), and T69S-XX was identified in two of the study samples (0.5%; both of them T69S-SS), but both patterns were absent among control samples. Non-NRTI (NNRTI)-related changes were observed in viral strains from two patients, which displayed the Q151M resistance pattern, although the patients were NNRTI naive. The patients whose isolates displayed multinucleoside resistance had received treatment with zidovudine and either didanosine, zalcitabine, or stavudine. Both resistance patterns conferred broad cross-resistance to NRTIs in vitro and a poor response to treatment in vivo. MNR HIV-1 is found only among multinucleoside-experienced patients. Its prevalence is low in Europe, but it should be closely monitored since it seriously limits treatment options.

TI Prevalence and characteristics of multinucleoside-resistant human immunodeficiency virus type 1 among European patients receiving combinations of nucleoside analogues.

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     STN
ACCESSION NUMBER:    2000:162317  BIOSIS
DOCUMENT NUMBER:     PREV200000162317
TITLE:               Prevalence of HIV-1 resistant to antiretroviral
                     drugs in 81 individuals newly infected by sexual contact or
                     injecting drug use.
AUTHOR(S):           Salomon, Horacio; Wainberg, Mark A. [Reprint author];
                     Brenner, Bluma; Quan, Yudong; Rouleau, Danielle; Cote,
                     Pierre; LeBlanc, Roger; Lefebvre, Eric; Spira, Bonnie;
                     Tsoukas, Chris; Sekaly, Rafik-Pierre; Conway, Brian;
                     Mayers, Douglas; Routy, Jean-Pierre; Investigators of the
                     Quebec Primary Infection Study
CORPORATE SOURCE:    McGill AIDS Centre, Lady Davis Institute/Jewish General
                     Hospital, 3755 Cote Ste-Catherine Road, Montreal, PQ, H3T
                     1E2, Canada
SOURCE:              AIDS (Hagerstown), (Jan. 28, 2000) Vol. 14, No. 2, pp.
                     F17-F23. print.
                     CODEN: AIDSET. ISSN: 0269-9370.
DOCUMENT TYPE:       Article
LANGUAGE:            English
ENTRY DATE:          Entered STN: 26 Apr 2000
                     Last Updated on STN: 4 Jan 2002
AB   Objective: Prolonged treatment with antiretroviral drugs results in the
     selection of HIV-1 variants with mutations conferring resistance to
     nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI and
     NNRTI) or to protease inhibitors (PI).  There is serious concern
     about transmission of resistant viruses to newly infected
     persons.  This study monitored the prevalence of resistant
     viruses in individuals undergoing primary HIV infection.  Design:
     Resistance testing was performed on 81 individuals infected between 1997
     and 1999 by injecting drug use (n = 21), sexual (n = 56), or unknown (n =
     4) transmission.  Methods: Automated sequencing was used to genotype the
     reverse transcriptase (RT) and protease regions of virus isolated from
     patients' plasma.  The phenotypic susceptibility of stimulated peripheral
     blood mononuclear cells to antiretroviral drugs was assayed.  Line probe
     assays detected quasispecies variations in wild-type and mutated RT
     codons.  Results: A high prevalence of PI and RT genotypic
     variants, associated with high-level resistance to antiretroviral drugs,
     was observed in individuals newly infected by injecting drug use (PI =
     24%, RT = 24%) or sexual transmission (PI = 12%, RT = 22%).  The PI
     mutations, L10I, V82A, and L90M, were found in 10.5, 3 and 4% of cases,
     respectively; whereas for RT, primary mutations at positions T215Y
     (zidovudine), M184V (lamivudine), T69D/A (zalcitabine), and K103N (multi-
     NNRTI) were present in 8, 5, 4, and 4% of subjects, respectively.
     Resistance to NRTI was demonstrated by phenotypic, genotypic, and line
     probe analyses.  Transmission of multidrug (NRTI/NNRTI/PI)
     resistance in eight subjects (9.9%) was confirmed by showing that source
     partners possessed viruses of similar genotype.  Conclusions: The
     transmission of drug-resistant HIV is a serious problem that
     merits further attention by public health officials as well as virologists
     and clinicians.
TI   Prevalence of HIV-1 resistant to antiretroviral drugs in 81
     individuals newly infected by sexual contact or injecting drug use.

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     STN
ACCESSION NUMBER:    1999:48446  BIOSIS
DOCUMENT NUMBER:     PREV199900048446
TITLE:               Biochemical characterization of HIV-1 reverse
                     transcriptases encoding mutations at amino acid residues
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                      161 and 208 involved in resistance to phosphonoformate.
AUTHOR(S):            Tramontano, Enzo [Reprint author]; Piras, Giovanna;
                      Mellors, John W.; Putzolu, Monica; Bazmi, Hengameh Z.;
                      Colla, Paolo La
CORPORATE SOURCE:     Dip. Biol. Sperimentale, Sezione Microbiol., Univ.
                      Cagliari, V.le Regina Margherita 45, 09124 Cagliari, Italy
SOURCE:               Biochemical Pharmacology, (Dec. 15, 1998) Vol. 56, No. 12,
                      pp. 1583-1589. print.
                      CODEN: BCPCA6. ISSN: 0006-2952.
DOCUMENT TYPE:        Article
LANGUAGE:             English
ENTRY DATE:           Entered STN: 10 Feb 1999
                      Last Updated on STN: 10 Feb 1999
AB    Mutations at amino acid residues 161 (Q161L) and 208 (H208Y) of the
      reverse transcriptase (RT) have been identified in HIV-1 variants which
      are resistant to phosphonoformate (PFA).  In the present study,
      we report on the biochemical properties of recombinant RTs (rRTs) carrying
      either one or both of the above mutations.  We also report on their
      susceptibility to PFA and to nucleoside (NRTI) and non-nucleoside (
      NNRTI) RT inhibitors.  Like the wild-type (wt) enzyme, mutant rRTs
      H208Y and Q161L/H208Y showed a preference for Mg2+ over Mn2+, whereas the
      Q161L rRT preferred Mn2+.  The three mutant rRTs showed degrees of PFA
      resistance which differed according to the template-primer used, and
      steady-state kinetic studies revealed an inverse correlation between their
      degree of PFA resistance, affinity for deoxynucleoside triphosphates
      (dNTPs) and catalytic efficiency (kcat/Km ratio).  These results indicated
      that HIV-1 rRTs bearing mutations at codons 161 and/or 208 had
      altered dNTP binding sites which led to a PFA-resistant
      phenotype.  However, unlike the corresponding mutant viruses, which are
      hypersensitive to 3'-azido-3'-deoxythymidine (AZT), 11-cyclopropyl-5,-11-
      dihydro-4-methyl-6H-dipyridol(3,2-b:2',3',-e)diazepin-6-one (Nevirapine)
      and (+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-
      imidazo(4,5,1-jk)(1,4)benzodiazepin-2(1H)-thione. (TIBO R82150), the
      mutant RTs Q161L and Q161L/H208Y were resistant to
      3'-azido-3'-deoxythymidine triphosphate (AZTTP) and as susceptible as the
      wt enzyme to Nevirapine and TIBO R82150.  Overall, these results suggest
      that codons 161 and 208 of the HIV-1 RT gene are involved in
      substrate binding as well as in NRT1 recognition, and provide more
      insights into the mechanism by which HIV-1 becomes resistant to
      PFA.
TI    Biochemical characterization of HIV-1 reverse transcriptases encoding
      mutations at amino acid residues 161 and 208 involved in resistance to
      phosphonoformate.

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      STN
ACCESSION NUMBER:     1996:103822  BIOSIS
DOCUMENT NUMBER:      PREV199698675957
TITLE:                Selective pressure of a quinoxaline nonnucleoside inhibitor
                      of human immunodeficiency virus type 1 (HIV-1) reverse
                      transcriptase (RT) on HIV-1 replication results in the
                      emergence of nucleoside RT-inhibitor-specific (RT Leu-74
                      fwdarw Val or Ile and Val-75 fwdarw Leu or Ile) HIV-1
                      mutants.
AUTHOR(S):            Kleim, Jorg-Peter [Reprint author]; Rosner, Manfred;
                      Winkler, Irvin; Paessens, Arno; Kirsch, Reinhard; Hsiou,
                      Yu; Arnold, Edward; Riess, Gunther
CORPORATE SOURCE:     General Pharma Res., Hoechst AG, D-65926 Frankfurt, Germany
SOURCE:               Proceedings of the National Academy of Sciences of the
                      United States of America, (1996) Vol. 93, No. 1, pp. 34-38.
                      CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE:        Article
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LANGUAGE:           English
ENTRY DATE:         Entered STN: 12 Mar 1996
                    Last Updated on STN: 10 Jun 1997
AB   The quinoxaline nonnucleoside RT inhibitor (NNRTI)
     (S)-4-isopropoxycarbonyl-6-methoxy-3-(methylthiomethyl)-3,4-
     dihydroquinoxaline-2(1H)-thione (HBY 097) was used to select for drug-
     resistant HIV-1 variants in vitro.  The viruses first developed
     mutations affecting the NNRTI-binding pocket, and five of six
     strains displayed the RT G190 fwdarw E substitution, which is
     characteristic for HIV-1 resistance against quinoxalines.  In one variant,
     a new mutant (G190 fwdarw Q) most likely evolved from preexisting G190
     fwdarw E mutants.  The negative charge introduced by the G190 fwdarw E
     substitution was maintained at that site of the pocket by simultaneous
     selection for V179-D together with G190 fwdarw Q.  After continued
     exposure to the drug, mutations at positions so far known to be specific
     for resistance against nucleoside RT inhibitors (NRTIs) (L74 fwdarw V/I
     and V75 fwdarw L/I) were consistently detected in all cultures.  The
     inhibitory activities of the cellular conversion product of
     2',3'-dideoxyinosine (ddI, didanosine), 2',3'-dideoxyadenosine (ddA) and
     of 2',3'-didehydro-3'-deoxythymidine (d4T, stavudine) against these
     late-passage viruses were shown to be enhanced with the L74 fwdarw V/1 RT
     mutant virus as compared with the wild-type (wt) HIV-1-MN isolate.  Clonal
     analysis proved linkage of the codon 74 and codon 75
     mutations to the NNRTI-specific mutations in all RT gene
     fragments.  The nonnucleoside- and nucleoside-resistance mutation sites
     are separated by approximately 35 ANG .  We propose that the two sites
     "communicate" through the template-primer which is situated in the
     DNA-binding cleft between these two sites.  Quinoxalines cause high
     selective pressure on HIV-1 replication in vitro; however, the implication
     of these findings for the treatment of HIV-1 infection has yet to be
     determined.
TI   Selective pressure of a quinoxaline nonnucleoside inhibitor of human
     immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) on HIV-1
     replication results in the emergence of nucleoside RT-inhibitor-specific
     (RT Leu-74 fwdarw Val or Ile and Val-75 fwdarw Leu or Ile) HIV-1 mutants.


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